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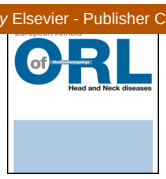

Case report

Epstein-Barr virus-associated lymphoepithelial carcinoma of the larynx

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ABSTRACT

Introduction: Lymphoepithelial carcinoma is a rare tumour, named after its histological resemblance to undifferentiated nasopharyngeal carcinoma. The pathogenesis of lymphoepithelial carcinoma remains unknown. This tumour has been described in several organs, but the larynx remains an exceptional site.
Case report: The authors report the case of a 73-year-old man who consulted for longstanding dysphonia and rapidly deteriorating dyspnoea requiring emergency tracheotomy. Endoscopic examination demonstrated a tumour of the left hemilarynx with fixed vocal cords. Histological examination and immunohistochemistry demonstrated lymphoepithelial carcinoma of the larynx. Screening for Epstein-Barr Virus (EBV) by immunohistochemistry and in situ hybridization was positive. Treatment consisting of neoadjuvant chemotherapy followed by surgical resection and then external beam radiotherapy achieved cure with a follow-up of 18 months since completion of treatment.
Discussion: Lymphoepithelial carcinoma of the larynx is rare. Immunohistochemical examination is essential for the positive diagnosis. Epstein-Barr virus-associated lymphoepithelial carcinoma has been exceptionally reported. The radiosensitivity of this tumour allows conservative first-line treatment.

1. Introduction

The most typical form of lymphoepithelial carcinoma is undifferentiated nasopharyngeal carcinoma [1,2]. More rarely, this tumour can arise in other sites, especially the salivary glands, thymus, lung and stomach [1,3], while laryngeal lymphoepithelial carcinoma is extremely rare, as only about thirty cases have been reported in the literature [1]. It represents 0.2% of all malignant tumours of the larynx [1,4,5].

We report a case of Epstein-Barr virus-associated lymphoepithelial carcinoma of the larynx and discuss the pathogenesis, clinical and pathological features and treatment of this tumour.

2. Case report

A 73-year-old man, with no notable history, presented with a 5-month history of dysphonia with recent onset of rapidly deteriorating dyspnoea, requiring emergency tracheotomy. Indirect laryngoscopy demonstrated a lesion of the left hemilarynx with fixed vocal cords. Neck examination revealed firm, mobile, deep cervical lymph nodes measuring 2 cm in diameter. Nasopharyngeal endoscopy was normal. CT scan of the neck demonstrated a left laryngeal tumour extending to the pre-epiglottic space and left paraglottic space with ipsilateral necrotic jugulo-carotid lymphadenopathy, with a long axis of 1.8 cm (Fig. 1). Direct laryngoscopy under general anaesthesia demonstrated a fungating lesion involving all of the left hemilarynx with infiltration of the pharyngolaryngeal wall. A biopsy was performed and histological examination showed a proliferation composed of moderately large to large syncytial cells with a vesicular nucleolated nucleus, basophilic or amphophilic cytoplasm and the presence of numerous mitotic figures. This tumour was surrounded by a lymphoid stroma composed of small regular lymphocytes (Fig. 2). Tumour cells expressed cytokeratin on immunohistochemistry. Screening for EBV by immunohistochemistry using anti-LMP 1 antibody (latent membrane protein 1) (Fig. 3A) and in situ hybridization using the EBER probe (Fig. 3B) was positive. EBV serology was in favour of old EBV infection (negative anti-VCA IgM, positive anti-VCA IgG, positive anti-EBNA IgG). The diagnosis adopted was that of EBV-associated lymphoepithelial carcinoma of the larynx. Staging assessment (chest X-ray, abdominal ultrasound, bone scan) was negative. As the tumour was classified as T3N1M0, it was decided to start treatment with neoadjuvant chemotherapy with a combination of cisplatin and adriamycin. After three cycles, the tumour

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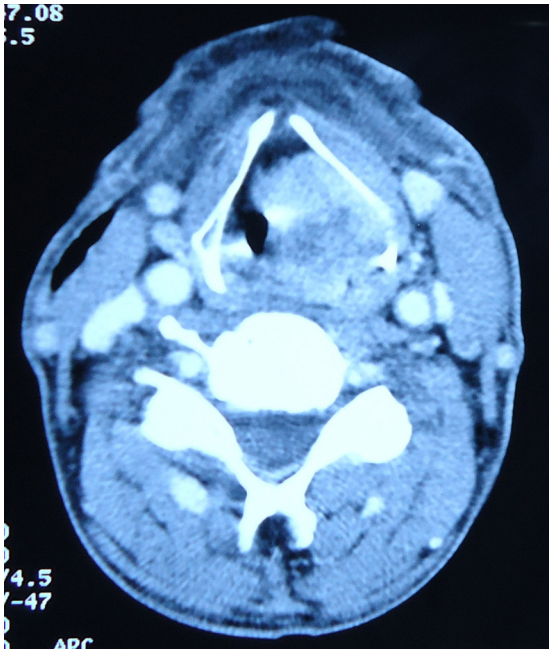

Fig. 1. CT scan of the neck, contrast-enhanced axial slice: heterogeneously enhanced left laryngeal tumour extending into the left paraglottic space.

response, estimated at 30%, was considered to be insufficient. The lymph node response was 50%. The patient was therefore operated by total pharyngolaryngectomy with bilateral functional neck dissection. Histological examination of the operative specimen confirmed left glottic and supraglottic invasion by lymphoepithelial carcinoma with healthy resection margins. Tumour invasion, without capsular rupture, was detected in one of the 18 lymph nodes of the left neck dissection (17 N–, 1 N + R–). None of the 13 nodes of the right neck dissection was metastatic (13 N–). External beam radiotherapy with cobalt 60 was administered postoperatively, delivering a dose of 54 Gy to the neck. The patient presented a favourable outcome with no signs of recurrence with a follow-up of 18 months since completion of treatment.

3. Discussion

Lymphoepithelial carcinoma of the larynx usually affects men between the ages of 50 and 70 years [1,5]. Clinical symptoms are dominated by dysphonia and dysphagia [1,6]. Lymph node invasion at the time of diagnosis is described in 75% of cases and systemic metastases are described in 29% of cases [1].

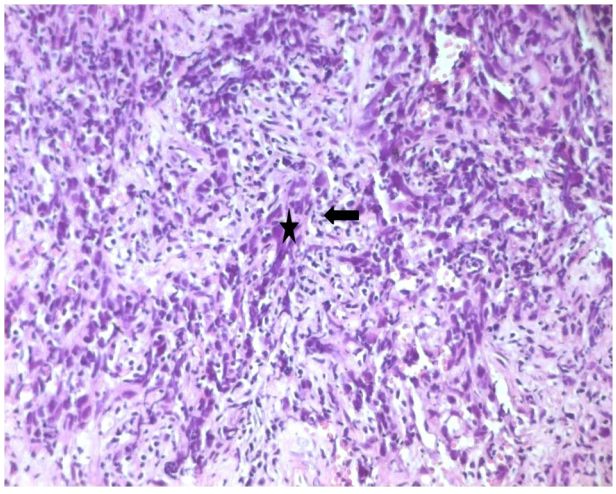

Fig. 2. Clump of undifferentiated malignant cells with a syncytial appearance (★), surrounded by a lymphocyte-rich stroma (⬅) (HE × 200).

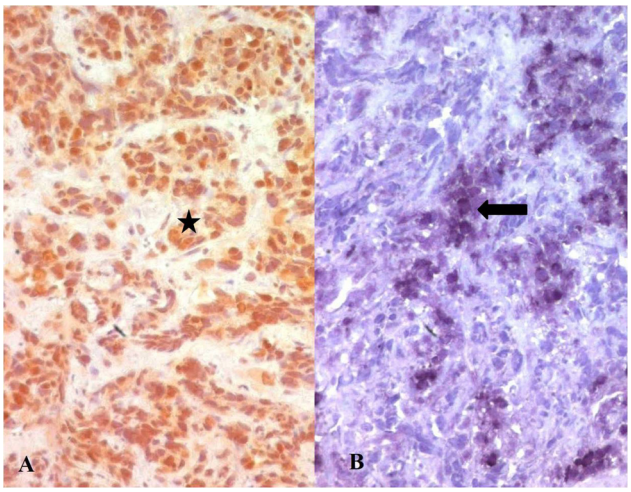

Fig. 3. A. Tumour cells are positive for LMP 1 (★) (latent membrane protein 1). B. In situ hybridization: tumour cells express EBV (⬅) (HE × 200).

On endoscopic examination, the tumour predominantly involves the laryngeal ventricle and spreads to the paraglottic and/or pre-epiglottic space [4,5,7] and can therefore have a misleading appearance with the tumour simply displacing the ventricular band or as ulceration of the epiglottic mucosa [4].

On histological examination, lymphoepithelial carcinoma of the larynx is composed of clumps or bands of moderately large to large undifferentiated cells with a syncytial appearance, vesicular nuclei, often with a high mitotic index. This tumour is surrounded by non-neoplastic lymphoid stroma, composed of small regular lymphocytes [3,4]. This histological description corresponds to type III of the WHO classification of nasopharyngeal carcinoma [4,8].

The histological diagnosis of lymphoepithelial carcinoma of the larynx can be difficult on biopsy and even on the operative specimen, as it raises a problem of differential diagnosis essentially with non-Hodgkin's lymphoma and malignant melanoma [1,3]. Immunohistochemistry is able to distinguish these lesions from lymphoepithelial carcinoma of the larynx by demonstrating expression of cytokeratin by tumour cells [1,3]. Nasopharyngeal carcinoma with laryngeal metastasis must also be eliminated.

The pathogenesis of lymphoepithelial carcinoma of the larynx remains unclear. The role of EBV infection, largely incriminated in the pathogenesis of nasopharyngeal lymphoepithelial carcinoma, is much more controversial in the case of lymphoepithelial carcinoma in other sites [6,8,9].

Only lymphoepithelial carcinomas of the salivary glands, thymus, lung and stomach are regularly associated with EBV [3,6,9]. In lung and salivary gland lymphoepithelial carcinomas, this association with EBV is only observed in South East Asian populations and Eskimos as in the case of salivary gland tumours [2,3,9]. In a review of the literature, based on 16 cases of lymphoepithelial carcinoma of the larynx, EBV screening was positive in only four patients [1]. In our case, screening for EBV by immunohistochemistry and in situ hybridization was strongly positive. To our knowledge, we therefore report the fifth case of EBV-associated lymphoepithelial carcinoma of the larynx. However, the presence of EBV in lymphoepithelial carcinoma does not appear to have a major prognostic significance [3,5].

In terms of treatment, the radiosensitivity of lymphoepithelial carcinoma allows conservative first-line treatment [1,4,7]. Surgery

is indicated for locally advanced tumours [4]. Chemotherapy ensures better distant disease control in patients with lymphadenopathy at the time of diagnosis [1,2,5].

4. Conclusion

Non-nasopharyngeal lymphoepithelial carcinomas of the head and neck are rare epithelial tumours. We report an exceptional case of EBV-associated lymphoepithelial carcinoma of the larynx. The positive diagnosis must be based on immunohistochemistry demonstrating cytokeratin expression to identify the poorly differentiated epithelial component. The role of EBV in the pathophysiology of this tumour cannot be clearly determined due to the small number of published cases. The radiosensitivity of lymphoepithelial carcinoma allows conservative first-line treatment.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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